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PCT

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(54) Title: <b>FORMULATIONS FOR STABILIZING OF IgM ANTIBODIES</b>			
(57) Abstract <p>Compositions suitable for intravenous injection are disclosed, which comprise a stabilizing buffer solution containing IgM antibodies. The compositions are effective in stabilizing the antibodies in solution, inhibiting precipitation and the formation of particulates in the final product vial, while maintaining a high level of immunoreactivity. The compositions can be lyophilized to form dry, stable products which can be readily reconstituted to provide injectable, particle-free antibody solutions.</p>			

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FORMULATIONS FOR  
STABILIZING OF IgM ANTIBODIES

Background of the Invention

It is well known that many protein preparations intended for administration to humans require stabilizers to prevent denaturation of the proteins, agglomeration and other alterations to the proteins prior to the use of the preparation. Many protein preparations are particularly unstable in dilute solutions. This instability is manifested in the formation of insoluble particles, and is often increased when the protein preparation is stored, or shipped. A major challenge that exists in the field of protein drugs is in the development of formulations that maintain both protein solubility and activity.

Immunoglobulins, in particular, are recognized as possessing characteristics that tend to form particulates in solution, requiring filtration of these formulations prior to using them for intravenous injection. The formation of protein aggregates and particulates has long been a problem in the development of parenteral immunoglobulin products. The administration of immunoglobulin G (IgG), for example, was limited to the intramuscular route because of endogenous anticomplementary activity due to aggregated immunoglobulin until the recent development of chemically and enzymatically treated immunoglobulin G. J. E.

Pennington, Rev. Inf. Dis., 8(4):5371-5373 (1986).

Recent modifications in immunoglobulin G formulations have helped to alleviate the problem. J. P. McCue et

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al., Rev. Inf. Dis., 8(4):5374-5381 (1986). However, most commercially available formulations now in use require filtration of the product prior to injection to remove these insoluble aggregates or particulates.

05       The immunoglobulin (IgM) isotype is the largest of the immunoglobulins, having a molecular weight of approximately 900,000 daltons. IgM molecules tend to be inherently unstable and precipitate readily upon being subjected to various forms of physical and chemical  
10 stress. This characteristic makes the formulation of a stable composition containing IgM intended for parenteral administration difficult.

#### Summary of the Invention

      The invention comprises stabilizing compositions  
15 for IgM antibodies. The present compositions contain a buffer, human serum albumin, sodium chloride, and IgM antibodies or antibody fragments. The compositions enhance the stability of IgM antibodies in solution intended for intravenous administration.

20       The present compositions can be lyophilized to form a dry powder. Lyophilization preserves the biological activity of the IgM antibody, and minimizes formation of particulates, which can occur in a liquid formulation under physical or chemical stress. The lyophilized  
25 product can be readily reconstituted to a particle-free solution which shows no loss of biological activity, and which can be administered without prior filtration.

      The present liquid and lyophilized formulations both exhibit superior stabilizing characteristics in  
30 terms of minimal protein particle formation, and

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preservation of immunoreactivity over time, and under stress conditions such as elevated temperatures, vial filling and shipping.

The present liquid and lyophilized compositions  
05 have both been successful in stabilizing IgM antibodies. The compositions maintain a particle-free, stable solution for injectable monoclonal antibodies and do not have to be filtered prior to administration. The lyophilized product, in particular, can be shipped and  
10 stored without loss of immunoreactivity. Neither formulation requires refrigeration or other special handling.

#### Brief Description of the Figures

Figure 1 shows gel filtration HPLC results  
15 comparing non-lyophilized and lyophilized/reconstituted IgM formulations and placebos.

Figure 2 is a diagram of the results of an immuno-reactivity assay comparing the ability of non-lyophilized and lyophilized/reconstituted IgM  
20 formulations to bind to solid phase lipid A.

#### Detailed Description of The Invention

The compositions of this invention minimize the formation of protein aggregates and particulates in reagents containing immunoglobulin M (IgM) antibodies  
25 and insure that the antibody in solution maintains its immunoreactivity over time. The preparation comprises a sterile, pharmaceutically acceptable solution containing tromethamine or phosphate buffer, having a neutral or

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basic pH (e.g., 6.8 or above), sodium chloride, IgM antibodies and human serum albumin.

05 Buffers have long been used to stabilize the pH of antibody products for parenteral injection. Protein solubility in the buffer solution depends upon a number of factors, such as ionic strength and pH of the solution.

10 Buffers which can be used for this formulation include tromethamine and phosphate buffers having a neutral or basic pH. Lower pH formulations showed less stability, i.e., a higher tendency to form aggregates. Tromethamine is described in the Merck Index, 10th edition, Merck and Co., Inc., Rahway, N.J. The concentration of tromethamine can be from about 5 to about 100 15 mM, having a pH from about 8 to about 10.

A phosphate buffer, such as sodium phosphate, can also be used. A concentration of from about 8 to about 20 mM phosphate can be used in the present composition, having a pH of from about 6.8 to about 7.4.

20 A stabilizing protein is added to the formulation. Stabilizing proteins are proteins which increase the solubility and/or stability of immunoglobulins in aqueous solutions. For example, when added to an aqueous solution of immunoglobulins, these proteins 25 prevent the immunoglobulins from precipitating out of the solution, thereby permitting higher concentrations of immunoglobulins to be solubilized. It has been found for the present compositions that human serum albumin (HSA) is a particularly useful stabilizer for IgM for 30 both liquid and lyophilized formulations. HSA is present in the formulation in an amount of about 2.5 to

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about 10% by weight per volume. Levels of HSA of from about 2.5% (w/v), to about 5% (w/v), are particularly effective in maintaining a stable solution of IgM.

In one embodiment of the invention stabilizing reagents for HSA, e.g., sodium caprylate and N-acetyl tryptophanate, are present in the formulation. HSA is less stable in solution (i.e., more likely to aggregate) in the absence of these compounds. For example, a 25% solution (w/v) of HSA contains 20 mM sodium caprylate and 20 mM N-acetyl tryptophanate, therefore, 2.5% (w/v) HSA added to a formulation includes 2 mM sodium caprylate and 2 mM N-acetyl tryptophanate. Other stabilizing reagents can be used other than N-acetyl tryptophanate and sodium caprylate, which are mentioned above for illustrative purposes.

Sodium chloride is added to the present composition to increase the ionic strength which is required for the solubility of the IgM proteins. IgM proteins are more soluble in an aqueous salt solution than in water alone. The amount of sodium chloride added is from about 200 to about 350 mM. About 270-300 mM sodium chloride is particularly effective for this purpose.

The present liquid and lyophilized compositions can be used to stabilize all subclasses of IgM antibodies, as well as IgM. The present compositions are particularly useful in stabilizing human monoclonal IgM antibodies.

One embodiment of this invention comprises a composition containing from about 5mM to about 100mM tromethamine (pH 8-10), from about 200 mM to about 300mM sodium chloride, from about 2.5 to about 5% (w/v) HSA and from about 2.5 to about 10.0mg/ml IgM antibody.



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Sodium caprylate in an amount of from about 2 mM to about 4 mM, and N-acetyl tryptophanate in an amount of from about 2 mM to about 4 mM can, optionally, be included to stabilize the HSA. A preferred embodiment of the invention comprises about 4.5 mM tromethamine (pH 8.5) about 270 mM sodium chloride, about 2.5% (w/v) HSA, about 5 mg/ml IgM antibodies or antibody fragments, and about 2 mM each of N-acetyl tryptophanate and sodium caprylate. This formulation enhances the stability of immunological activity of the monoclonal antibody, and prevents the immunoglobulins in solution intended for intravenous administration to human subjects from precipitating and forming particulates in the final product vial.

Another embodiment of the present invention comprises a composition containing from about 8 mM to about 20 mM of sterile, pyrogen-free sodium phosphate (pH 6.8-7.4), from about 250 mM to about 350 mM sodium chloride, from about 2.5 to about 5% (w/v) HSA and from about 2.5 to about 10.0 mg/ml IgM antibody or antibody fragments. Sodium caprylate and N-acetyl tryptophanate may be included in the formulation in the amount of about 2 mM to about 4 mM of each. A preferred embodiment of this formulation comprises about 8 mM sodium phosphate (pH 7.2), about 270 mM sodium chloride, about 5.0% (w/v) human serum albumin, about 5 mg/ml IgM antibodies or antibody fragments, and about 2 mM each of sodium caprylate and N-acetyl tryptophanate.

In another embodiment of the present invention, the above formulations can be lyophilized to form a dry, storable powder, which can be easily reconstituted to a

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particle free solution suitable for intravenous injection. Lyophilization is a freeze drying process which is often used in the preparation of pharmaceutical products to preserve their biological activity. The liquid composition is prepared, then lyophilized to form a dry cake-like product. The process generally involves drying a previously frozen sample in a vacuum to remove the ice, leaving the non-water components intact, in the form of a powdery or cake-like substance. The lyophilized product can be stored for prolonged periods of time, and at elevated temperatures, without loss of biological activity, and can be readily reconstituted into a particle-free solution by the addition of an appropriate diluent. An appropriate diluent can be any liquid which is biologically acceptable and in which the lyophilized powder is completely soluble. Water, particularly sterile, pyrogen-free water, is the preferred diluent, since it does not include salts or other compounds which may affect the stability of the antibody. The advantage of lyophilization is that the water content is reduced to levels which greatly reduce the various molecular events which lead to instability of the product. The lyophilized product is also better able to withstand the physical stresses of shipping. The reconstituted product is particle free, so it can be administered intravenously without prior filtration.

The present invention is further illustrated by the following Examples, which is not intended to be limiting in any way.

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EXAMPLE 1Preparation of IgM Liquid and Lyophilized Formulations  
Based On TromethamineLiquid Formulation

05 IgM (HA-1A IgM, lot # 012567, Centocor, Inc.,  
Malvern, PA) was concentrated to 5.5 mg/ml using a  
Centriprep 30 Concentrator (Amicon). The concentrated  
protein (20 ml) was dispensed into a 25 ml graduated  
cylinder and 2 ml of HSA containing sodium caprylate and  
10 N-acetyl tryptophanate (U.S.P. 25% HSA in 20 mM sodium  
caprylate and 20 mM N-acetyl tryptophanate, Armour  
Pharmaceutical Co.), tromethamine (50 mM, pH 8.50) and  
300 mM sodium chloride (NaCl) were added. The solution  
was filtered with a 0.2 $\mu$  syringe filter into a 50 ml  
15 centrifuge tube. Sodium azide ( 0.22 ml of 10%  
solution) was added to a final concentration of 0.1%.  
The final solution, was a clear, light yellow liquid  
composed of 4.95 mg/ml IgM, 45 mM tromethamine (pH  
8.35), 270 mM sodium chloride, 2.5% HSA, 2 mM sodium  
20 caprylate and 2 mM N-acetyl tryptophanate.

A "placebo" formulation was also made, which was  
exactly the same as the above formulation except that  
the IgM was left out. Thus, the placebo formulation  
contained 45 mM Tris buffer (pH 8.35), 270 mM NaCl, 2.5%  
25 HSA, 2 mM sodium caprylate and 2 mM N-acetyl trypto-  
phanate.

Lyophilization

The liquid IgM formulation was dispensed in 1 ml  
increments into 2 ml Type 1 Tubing vials (West Co.). A  
30 total of 20 vials were filled. The vials were placed in

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a lyophilizer (FTS) having a 1' x 1' shelf. In order to generate a full thermal load, the remainder of the shelf space was loaded with placebo vials.

The vials were capped with 13 mm gray butyl  
05 lyophilization closures (#224142, Wheaton). The shelves of the lyophilizer were prechilled to about 5°C, ± 2°C. The test vials and placebo vials were loaded onto a shelf in a tray, and a slight vacuum was induced in the chamber to maintain a good door seal. A total of 20  
10 vials of product and 355 vials of placebo were filled to occupy the entire shelf space.

After the vials had reached and maintained 5°C for at least 1 hour, the shelf surface temperature was set for about -40°C. ~~The vials were allowed to remain at~~  
15 -40°C for at least one hour. The condenser was chilled to about -70°C. The pressure in the chamber was reduced by means of a mechanical pump to less than 50 Torr. The shelf surface temperature was regulated such that the product temperature remained between -47°C and -42°C.  
20 After the product temperature had reached and maintained the shelf temperature for at least one hour, a mass spectrum of the residual gasses in the chamber was recorded. The shelf surface temperature was then set for about +20°C. When the temperature reached and  
25 maintained +20°C for at least 2 hours, the partial pressures of the residual gasses in the chamber was recorded.

The chamber was then backfilled with dry nitrogen to a pressure of about 600 Torr. The product was  
30 removed from the dryer and crimp seals were applied to

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the vials. The formulated protein formed a very dense cake upon freezing.

The lyophilized cakes that were formed did not possess any crust or glaze on the surface, and were 05 uniform throughout the vial.

#### Reconstitution of Lyophilized IgM

The crimp seals were removed from the vials to expose the closure, and the closure was removed from one vial containing the product and one placebo vial. A 10 sterile pipette was filled with 1.0 ml of sterile/pyrogen-free (s/pf) water (McGaw), which was dispensed into the vial holding the lyophilized product. Once all of the water was injected, the length of time necessary to dissolve all visually observable material 15 was measured:

#### Reconstitution Times

<u>Placebo</u>	<u>Product</u>
0.5 minutes	0.3 minutes

#### Visual Examination After Reconstitution

20 The vials were held directly in front of a black background for visual examination. This was accomplished by placing a light source below the vial so that the beam of light proceeded upwards through the liquid. Changes in color, turbidity, flocculation, fine precipi- 25 tation or any other particulate matter were examined. No discernable difference could be seen between the non-lyophilized formulation and the lyophilized

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reconstituted formulation. The results are shown in the following Table:

Visual Particle & Cosmetic Analysis

<u>Vial</u>	<u>Appearance</u>
05 Placebo (non-lyophilized)	clear, yellowish liquid
Product (non-lyophilized)	clear, yellowish liquid
Placebo (lyophilized)	clear, yellowish liquid
Product (lyophilized)	clear, yellowish liquid

HPLC Gel Filtration

10 The lyophilized product and placebo were measured by HPLC (Waters) gel filtration. Non-lyophilized product and placebo were also run. A DuPont Zorbax GF-450 gel column was equilibrated with a mixture of 0.2M sodium phosphate buffer (pH 6.8) and 0.3 M NaCl at a flow rate 15 of 1 ml/min. Absorbance wavelength was set for 214 nm.

One  $\mu$ l of undiluted sample (lyophilized and pre-lyophilized product and placebo) was injected onto the column through an automatic injector and run for 15 minutes. The results, shown in Figure 1, indicated no 20 detectable difference between the pre-lyophilized placebo and product and lyophilized/reconstituted placebo and product.

Immunoactivity Assay

The immunological activity of the IgM in each 25 formulation was determined using an enzyme-linked immunoassay to measure binding to solid-phase lipid A.

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A vial of Salmonella minnesota R595 lipid A (List Biological Laboratories, Inc., Campbell, CA; catalog #401) was reconstituted to 1 mg/ml with 0.5% TEA (triethylamine) in s/pf water. A 10 µg/ml solution of lipid A was made in a buffer solution consisting of 10 mM HEPES and sterile/pyrogen-free 0.9% NaCl (s/pf saline, McGraw), pH 7.2 (Buffer #1). This formulation was then dispensed into a PVC microtiter plate (Dynatech Laboratories, Inc., Chantilly, VA catalog #011-010-2101), 50 µl/well, and the plate was covered and incubated overnight at 4°C.

The plates were removed from the incubator and washed three times with s/pf saline, then blocked by dispensing 200 µl/well of a buffer consisting of: 10 mM HEPES, s/pf saline and 2% heat-inactivated FBS, pH 7.2 (Buffer #2). The plates were covered and incubated for 1 hour at 37°C. After incubation, the plates were washed three times with s/pf saline.

Solutions were prepared of the test formulations, an IgM standard and a negative control of human myeloma IgM (Chrompure Human Myeloma IgM, Jackson Immuno Research Laboratories, West Grove, PA) at a concentration of 5.0 µg/ml.

Buffer #2 was dispensed into the wells in rows B-H (50 µl/well). The IgM standard was dispensed into row A, columns 1-3 (100 µl/well). Test formulations were dispensed in triplicate in row A, columns 4-12 (100 µl/well). Serial 50µl dilutions were then made down the rows of the plate to row H. 50 µl of the 100 µl in row H was discarded, and the negative control was added.

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The plate was covered and incubated for 2 hours at 37°C, then washed three times with s/pf saline.

Substrate solution was prepared by adding 1 phosphatase substrate table (Sigma Chemicals, Inc., St. Louis, MO) to 5 ml of s/pf water containing a 1:500 dilution of an alkaline buffer solution (Sigma Chemicals, catalog #014-105), and incubated for 20 minutes. The reaction was stopped by adding 50 µl of 3M NaOH.

The optical density of the solutions were measured at 414 nm or using a plate reader. The data were analyzed using a 4 parameter fit of OD versus concentration.

The results, shown in Figure 2, indicated no detectable difference between the activity of the prelyophilized and lyophilized product.

#### Temperature Stress Testing

Lyophilized product samples were stored at 4°C, 22°C and 40°C. The samples were evaluated periodically for activity and appearance (i.e., particulate formation). The samples were reconstituted prior to evaluation. The results are shown in the following table:

<u>Temperature/Time</u>	<u>Activity</u>	<u>Appearance</u>
4°C/2 months	no change	clear
22°C/2 months	no change	clear
40°C/2 months	slight decrease	some particulates
4°C/5 months	no change	clear



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22°C/5 months	no change	clear
4°C/7 months	no change	clear

Equivalents

05 Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

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CLAIMS

1. A composition for IgM antibodies comprising a buffer, human serum albumin, sodium chloride, and IgM antibodies.
- 05 2. A composition of Claim 1, wherein the buffer comprises phosphate buffer or tromethamine.
3. A composition of Claim 2, wherein the phosphate buffer comprises sodium phosphate having a concentration from about 8 mM and about 20 mM and having  
10 a pH from about 6.8 to about 7.4.
4. A composition of Claim 2, wherein the tromethamine buffer has a concentration from about 5 to about 100 mM and a pH from about 8 to about 10.
5. A composition of Claim 1, wherein the concentration  
15 of sodium chloride is about 270 mM.
6. A composition of Claim 1 further comprising N-acetyl tryptophanate and sodium caprylate.
7. A composition of Claim 7, wherein the concentration of N-acetyl tryptophanate is from about 2 mM to  
20 about 4 mM and the concentration of sodium caprylate is from about 2 mM to about 4 mM.
8. A composition of Claim 1, wherein the concentration of IgM antibodies is about 5.0 mg/ml.

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9. A composition of Claim 8, wherein the IgM antibodies are human immunoglobulin.
10. A composition of Claim 1, wherein the IgM antibodies are monoclonal antibodies.
- 05 11. A composition of Claim 1 containing from about 2.5% to about 5% (w/v) human serum albumin.
12. A composition of Claim 1 which is lyophilized.
13. A composition of Claim 12 comprising a dry powder which can be reconstituted to yield an injectable  
10 solution of IgM.
14. An injectable composition for IgM, which comprises:
  - a. about 5 mM to about 100 mM tromethamine having a pH of from about 8 to about 10;
  - b. about 200 to about 300 mM sodium chloride;
  - 15 c. about 2.5 to about 5% weight per volume human serum albumin; and
  - d. about 2.5 to about 10.0 mg/ml of IgM antibodies.
15. An injectable composition of Claim 14, further  
20 comprising about 2 mM to about 4 mM sodium caprylate and about 2 mM to about 4 mM N-acetyl tryptophanate.
16. A composition of Claim 15 which comprises:
  - a. 45 mM tromethamine, pH 8.5;
  - 25 b. 270 mM sodium chloride;

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- c. 2.5% weight per volume human serum albumin;
- d. 5 mg/ml IgM antibodies;
- e. 2 mM sodium caprylate; and
- f. 2 mM N-acetyl tryptophanate.

05 17. A composition of Claim 16 which is lyophilized.

18. A composition of Claim 17 comprising a dry powder which can be reconstituted to yield an injectable solution of IgM.

19. An injectable composition of IgM, which comprises:

- 10 a. about 8 mM to about 20 mM sodium phosphate, having a pH of from about 6.8 to about 7.4;
- b. about 250 to about 350 mM sodium chloride;
- c. about 2.5 to about 5.0% weight per volume human serum albumin; and
- 15 d. about 2.5 to about 10.0 mg/ml of IgM antibodies.

20. An injectable composition of Claim 19, further comprising about 2 mM to about 4 mM sodium caprylate and about 2 mM to about 4 mM N-acetyl tryptophanate.

21. A composition of Claim 20 which comprises:

- a. 8 mM sodium phosphate, pH 7.2;
- b. 270 mM sodium chloride;
- c. 5.0% weight per volume human serum albumin;
- 25 d. 5 mg/ml IgM antibodies;
- e. 2 mM sodium caprylate; and

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f. 2 mM N-acetyl tryptophanate.

22. A composition of Claim 21 which is lyophilized.

23. A composition of Claim 22 comprising a dry powder  
which can be reconstituted to yield an injectable  
05 solution of IgM.

24. In an IgM composition containing buffer, protein  
and IgM, the improvement comprising combining the  
IgM antibodies with phosphate or tromethamine  
buffer, sodium chloride, and human serum albumin.

10 25. An improved composition of Claim 24, wherein the  
human serum albumin is stabilized with N-acetyl  
tryptophanate and sodium caprylate.

26. An improved composition of Claim 24, comprising:  
15 a. about 5 mM to about 100 mM tromethamine having  
a pH of from about 8 to about 10;  
b. about 200 to about 300 mM sodium chloride;  
c. about 2.5 to about 5% (w/v) human serum  
albumin;  
20 d. about 2.5 to about 10.0 mg/ml of IgM  
antibodies.  
e. about 2 mM to about 4 mM sodium caprylate; and  
f. about 2 mM to about 4 mM N-acetyl  
tryptophanate.

27. An improved composition of Claim 24 comprising:

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- a. about 8 mM to about 20 mM sodium phosphate;
  - b. about 250 to about 350 mM sodium chloride;
  - c. about 2.5 to about 5.0% (w/v) human serum albumin;
  - 05 d. about 2.5 to about 10.0 mg/ml of IgM antibodies;
  - e. about 2 mM to about 4 mM sodium caprylate; and
  - f. about 2 mM to about 4 mM N-acetyl tryptophanate.
- 10 28. An improved composition of Claim 26 which is lyophilized to a dry powder, which powder can be reconstituted to yield an injectable solution of IgM.
- 15 29. An improved composition of Claim 27 which is lyophilized to a dry powder, which powder can be reconstituted to form an injectable solution of IgM.

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Placebo:  
Pre Lyophilized

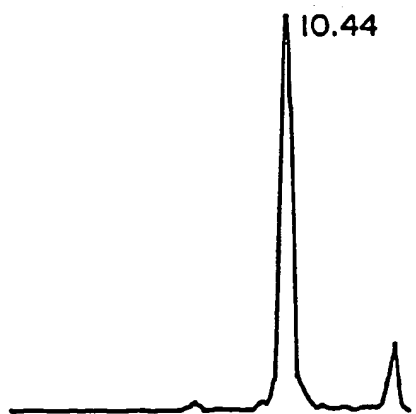


FIG. 1A

Placebo:  
Lyophilized/Reconstituted

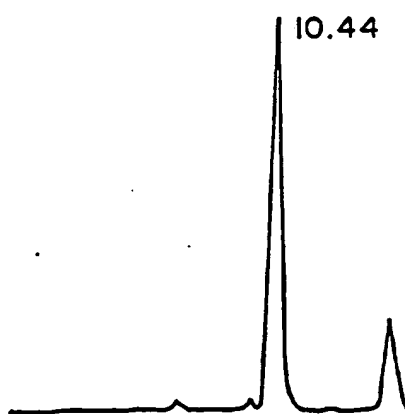


FIG. 1B

Product:  
Pre Lyophilized

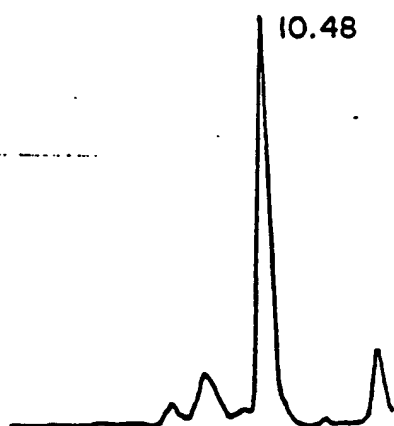


FIG. 1C

Product:  
Lyophilized/Reconstituted

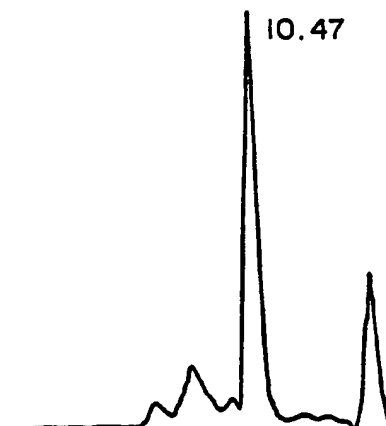


FIG. 1D

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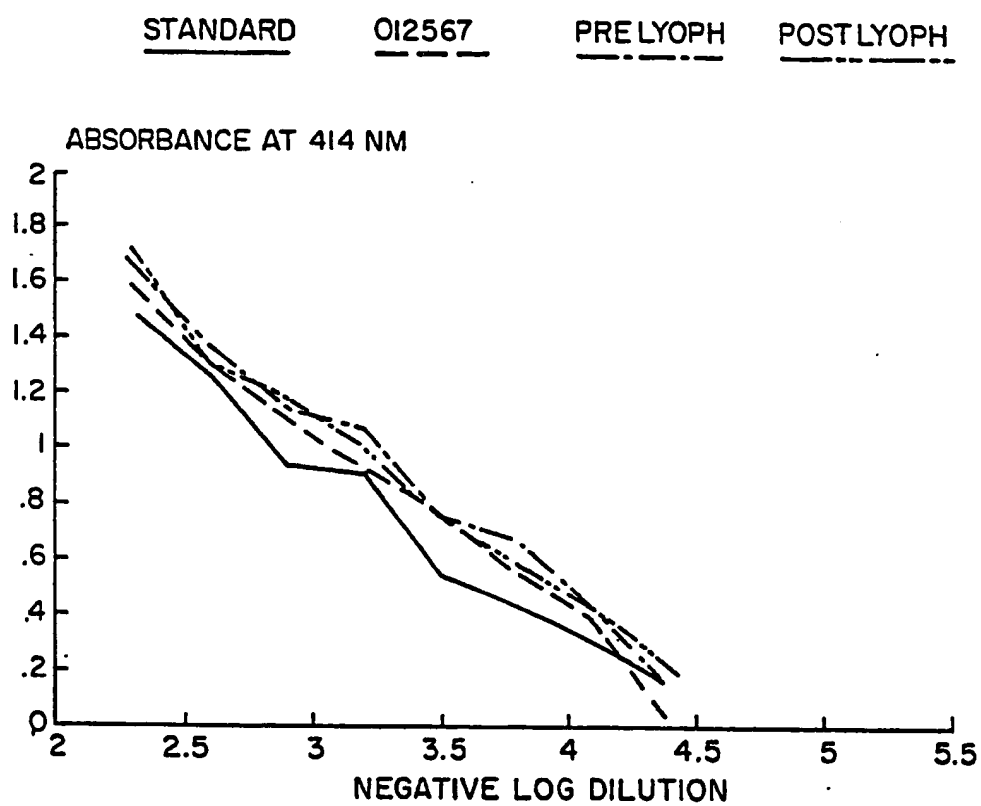


FIG. 2

SUBSTITUTE SHEET



# INTERNATIONAL SEARCH REPORT

International Application No **PCT/US 90/01383**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>5</sup> : A 61 K 39/395, A 61 K 47/42		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC <sup>5</sup>	A 61 K	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT *</b>		
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP, A, 0303088 (MILES INC.) 15 February 1989 see columns 4,5; example 1	1-29
X	Chemical Abstracts, volume 109, no. 16, 17 October 1988, (Columbus, Ohio, US), see page 378, abstract 134999k, & CS, A, 249222 (STACHY et al.) 15 March 1988 see the abstract --	1-29
A	GB, A, 2001325 (THE GREEN CROSS CORP.) 31 January 1979 --	
A	GB, A, 1546177 (BIOKEMA) 16 May 1979 -----	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
28th. June 1990	19. 07. 90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	<div style="display: flex; align-items: center;"> <div style="margin-right: 20px;"> </div> <div style="border: 1px solid black; padding: 2px 5px;">M. PEIS</div> </div>	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82